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Titlel: Diphenylurea derivatives and their use as chloride channel blockers

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This is to certify that the attached documents are exact copies of the above mentioned patent application as originally filed.

Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

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Pia Høybye-Olsen

PATENT- OG VAREMÆRKESTYRELSEN

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DIPHENYLUREA DERIVATIVES AND THEIR USE AS CHLORIDE CHANNEL BLOCKERS

TECHNICAL FIELD

The present invention relates to novel diphenylurea derivatives useful as chloride channel blockers.

In other aspects the invention relates to the use of these compounds in a method for therapy, and to pharmaceutical compositions comprising the compounds of the invention.

BACKGROUND ART

Chloride channels serve a wide variety of specific cellular functions and contribute to the normal function of i.a. skeletal and smooth muscle cells. Chloride channels are probably found in every cell, from bacteria to mammals. Their physiological tasks range from cell volume regulation to stabilization of the membrane potential, transepithelial or transcellular transport and acidification of intracellular organelles.

WO 97/45400, WO 98/47879, WO 00/20378 and WO 00/24707 (all NeuroSearch A/S) describe compounds, such as substituted phenyl derivatives, active as chloride channel blockers.

However, there is a continued strong need to provide compounds with an optimized pharmacological profile. Furthermore, there is a strong need to find effective compounds without unwanted side effects associated with older compounds.

SUMMARY OF THE INVENTION

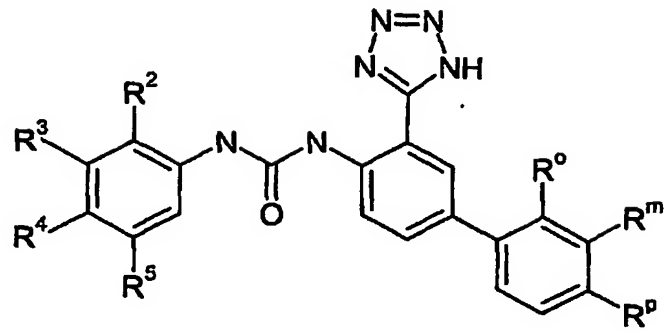
It is an object of the invention to provide novel compounds which act as chloride channel blockers.

A further object of the invention is the provision of compounds with a better selectivity. A still further object is the provision of compounds with a better potency.

A further object of the invention is the provision of compounds that act on cell or tissue specific chloride channels. A still further object is the provision of compounds that act on specific groups or subtypes of chloride channels.

A still further object is the provision of compound with more optimal pharmacodynamic properties such as kinetic behaviour, bioavailability, solubility and efficacy.

In its first aspect, the invention provides a compound of general formula I,



(I)

or a pharmaceutically acceptable salt thereof, wherein R^o, R^m, R^p, R^2, R^3, R^4 and R^5 are as defined below.

In its second aspect, the invention provides a pharmaceutical composition, comprising a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

In a further aspect, the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to the blockade of chloride channels.

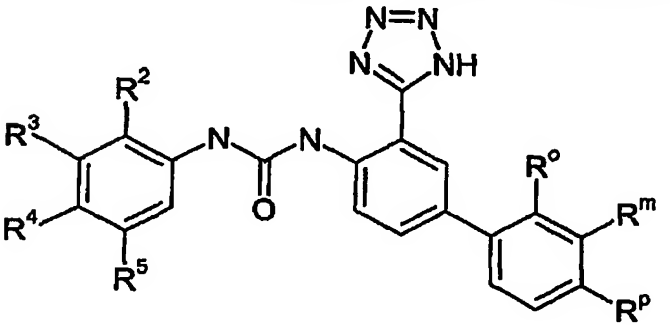
In a still further aspect, the invention relates to a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to responsive to blockade of chloride channels, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

Diphenylurea derivatives

In its first aspect, the invention provides a compound of general formula I,



(I)

or a pharmaceutically acceptable salt thereof, wherein

R^o, R^m and R^p independently of each other represent

hydrogen, halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy;

with the proviso that not all three of R^o, R^m and R^p represent hydrogen;

R^2, R^3, R^4 and R^5 independently of each other represent

hydrogen, halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy;

with the proviso that the compound is not

N-(3-Trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea.

In one embodiment of the compound of general formula I, R^o represents hydrogen; R^m represents hydrogen; and R^p represents halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy. In a special embodiment, R^p represents halo, such as chloro or fluoro, or bromo. In a further embodiment, R^p represents trifluoromethyl. In a still further embodiment, R^p represents trifluoromethoxy. In a further embodiment, R^p represents alkyl, such as methyl. In a still further embodiment, R^p represents alkoxy, such as methoxy.

In a further embodiment of the compound of general formula I, R^o represents hydrogen; R^p represents hydrogen; and R^m represents halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy. In a special embodiment, R^m represents trifluoromethyl.

In a further embodiment of the compound of general formula I, R^3, R^4 and R^5 represent hydrogen; and R^2 represents halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy. In a special embodiment, R^2 represents halo, such as chloro, fluoro or bromo. In a further embodiment, R^2 represents trifluoromethyl.

In a still further embodiment of the compound of general formula I, R^2, R^4 and R^5 represent hydrogen; and R^3 represents halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy. In a special embodiment, R^3 represents trifluoromethyl. In a further embodiment, R^3 represents halo, such as bromo.

In a further embodiment of the compound of general formula I, R^2, R^3 and R^5 represent hydrogen; and R^4 represents halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy. In a special embodiment, R^4 represents halo, such as chloro.

In a still further embodiment of the compound of general formula I, two of R^2, R^3, R^4 and R^5 represent hydrogen, and the other two of R^2, R^3, R^4 and R^5 independently of each other represent halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy.

In a still further embodiment of the compound of general formula I, R^2 and R^5 represent hydrogen; and R^3 and R^4 independently of each other represent halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy. In a special embodiment, R^3 represents trifluoromethyl. In a further embodiment, R^4 represents halo, such as chloro

or fluoro. In a still further embodiment, R^3 represents trifluoromethyl and R^4 represents chloro. In a further embodiment, R^3 represents trifluoromethyl and R^4 represents fluoro.

In a still further embodiment of the compound of general formula I, R^2 and R^4 represent hydrogen; and R^3 and R^5 independently of each other represent halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy. In a special embodiment, R^3 represents trifluoromethyl. In a further embodiment, R^3 represents halo, such as chloro or fluoro. In a still further embodiment, R^5 represents trifluoromethyl. In a further embodiment, R^5 represents halo, such as chloro or fluoro. In a still further embodiment, R^3 represents chloro and R^5 represents chloro. In a further embodiment, R^3 represents fluoro and R^5 represents fluoro. In a still further embodiment, R^3 represents trifluoromethyl and R^5 represents trifluoromethyl.

In a special embodiment the compound of the invention is

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[3-(1H-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;

N-(3-Trifluoromethyl-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(3,5-Dichloro-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(3,5-Difluoro-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(3,5-Dichloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;

N-(3,5-Difluoro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;

N-(3-Trifluoromethyl-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-5-yl]-urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(3,5-Dichloro-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(3,5-Difluoro-phenyl)-*N'*-[4'-fluoro-2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N- (4-Fluoro-3-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;

N-(2-Trifluoromethyl-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Bromo-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(2-Trifluoromethyl-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Bromo-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Bromo-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Fluoro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(2-Fluoro-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Fluoro-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Fluoro-phenyl)-*N'*-[4'-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Chloro-phenyl)-*N'*-[4'-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Bromo-phenyl)-*N'*-[4'-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Trifluoromethyl-phenyl)-*N'*-[4'-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Chloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(2-Chloro-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Chloro-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Dichloro-phenyl)-*N'*-[4'-methoxy-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Difluoro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethoxy-biphenyl-4-yl]-urea;
N-(3,5-Dichloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethoxy-biphenyl-4-yl]-urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethoxy-biphenyl-4-yl]-urea;
N-(3,5-Difluoro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(3,5-Dichloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(3,5-Difluoro-phenyl)-*N'*-[4'-methoxy-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4'-methoxy-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3-Bromo-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(4-Chloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N- (4-Fluoro-3-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea;
or a pharmaceutically acceptable salt thereof.

Definition of Substituents

In the context of this invention halo represents fluoro, chloro, bromo or iodo.

Alkyl means a straight chain or branched chain of one to six carbon atoms, including but not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and hexyl; methyl, ethyl, propyl and isopropyl are preferred groups.

Alkoxy is O-alkyl, wherein alkyl is as defined above.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate derived, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

Examples of pharmaceutically acceptable cationic salts of a chemical compound of the invention include, without limitation, the sodium, the potassium, the calcium, the magnesium, the lithium, and the ammonium salt, and the like, of a chemical compound of the invention containing an anionic group. Such cationic salts may be formed by procedures well known and described in the art.

Methods of Preparation

The compounds of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of a compound of the invention.

While a compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a

pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising a compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route, which suit the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by any skilled person by use of standard methods and conventional techniques appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

Biological Activity

The compounds of the present invention are useful as blockers of chloride channels, such as Volume regulated anion channels (VRAC) or chloride channels of osteoclasts. For measuring the activity of the compounds, various chloride channel blocking assays known in the art can be used.

Methods of Therapy

Compounds that are active as chloride channels blockers are likely to be useful in the treatment of a number of diseases, disorders and conditions, including bone metabolic diseases, or diseases, disorders or conditions which are responsive to inhibition of angiogenesis.

Thus in a further aspect, the compounds of the invention are considered useful for the treatment, prevention or alleviation of a disease, disorder or condition responsive to the blockade of chloride channels.

In a special embodiment, the disease or a disorder or a condition is a bone metabolic disease, such as an osteoclast related bone disease. In a further embodiment, the disease or a disorder or a condition is an osteoclast related bone disease, such as osteoporosis, postmenopausal osteoporosis, secondary osteoporosis, osteolytic breast cancer bone metastasis, osteolytic cancer invation, and Paget's disease of bone.

The diseases, disorders or conditions that are responsive to inhibition of angiogenesis include but are not limited to:

- diseases, disorders or conditions that involve the proliferation of tumor cells, such as cancer, prostate cancer, lung cancer, breast cancer, bladder cancer, renal cancer, colon cancer, gastric cancer, pancreatic cancer, ovarian cancer, melanoma, hepatoma, sarcoma and lymphoma;
- ophthalmic angiogenesis related diseases, disorders or conditions, such as exudative macular degeneration, age-related macular degeneration (AMD), retinopathy, diabetic retinopathy, proliferative diabetic retinopathy, diabetic macular edema (DME), ischemic retinopathy (e.g. retinal vain or artery occlusion), retinopathy of prematurity, neovascular glaucoma, and corneal neovascularization; and
- rheumatoid arthritis, and psoriasis.

In a special embodiment, the disease, disorder or condition to be treated is a preneoplastic disease state. In a further embodiment, the treatment is an anti-metastatic treatment. In a still further embodiment, the disease, disorder or condition to be prevented is metastatic cancer.

In a further embodiment, the disease or a disorder or a condition is sickle-cell anaemia.

Also, chloride channels blockers are likely to be useful in the treatment of a disease, disorder or condition that is responsive to reduction of intraocular pressure, such as ocular hypertension, open-angle glaucoma, chronic open-angle glaucoma, angle-closure glaucoma and ciliary injection caused by angle-closure glaucoma.

It is at present contemplated that suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily,

dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge. When administered in combination with compounds known in the art for treatment of the diseases, the dosis regimen may be reduced.

Combined therapy

Use of the compounds of the invention may be combined with the use of other compounds useful for the treatment, prevention or alleviation of a disease, disorder or condition responsive to the blockade of chloride channels.

As an example, the compounds may be used in combination with one or more additional drugs useful for the treatment, prevention or alleviation of a disease responsive to inhibition of angiogenesis, such as compounds useful for anti-metastatic treatment. Such additional drugs include cytotoxic compounds, antimitotic compounds, and antimetabolites.

Examples of cytotoxic compounds (including cytotoxic alkylating agents) include carmustine (BCNU), fotemustin, temozolomide (temodal), ifosfamide, and cyclofosfamide.

Examples of antimitotic compounds include paclitaxel (taxol) and docetaxel.

An example of antimetabolites includes methotrexat.

Furthermore, the pharmaceutical composition for use according to the invention may be used or administered in combination with other treatments or therapies. Examples of other treatments or therapies include radiotherapy and surgery.

Also, use of the compounds of the invention may be combined with the use of other bone metabolism controlling compounds for the treatment of bone metabolic disease. Such known bone metabolism controlling compounds include bisphophonates such as etidronate, pamidronate, or clodronate optionally combined with calcium; oestrogen-receptor active compounds such as oestrogen i.e. oestradiol and ethyloestradiol, calcitonin, 1,25-dihydroxyvitamine D and metabolites thereof, fluoride, growth hormone, parathyroid hormone, triiodo-thyrosine, collagen degrading enzymes such as protease inhibitors, or cancer therapeutic agents.

Also, use of the compounds of the invention may be combined with the use of one or more additional drugs useful for the treatment, prevention or alleviation of a disease, disorder or condition is responsive to reduction of intraocular pressure. Such additional drugs include beta-blockers, parasympathomimetic miotics, sympathomimetics, and carbonic anhydrase inhibitors.

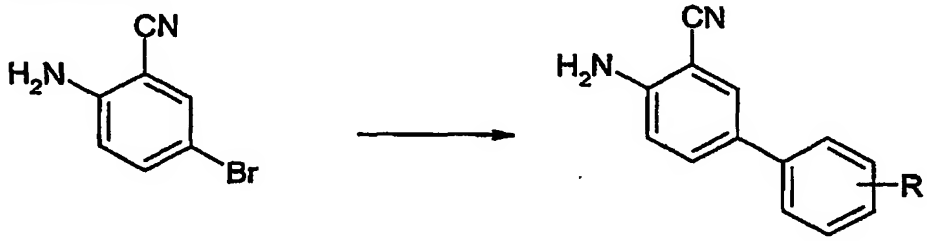
Furthermore, use of the compounds of the invention may be combined with other treatments or therapies.

The treatment of the diseases and disorder can be in chronical or a long term treatment as well as a treatment of sudden crisis in the disease and disorder.

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

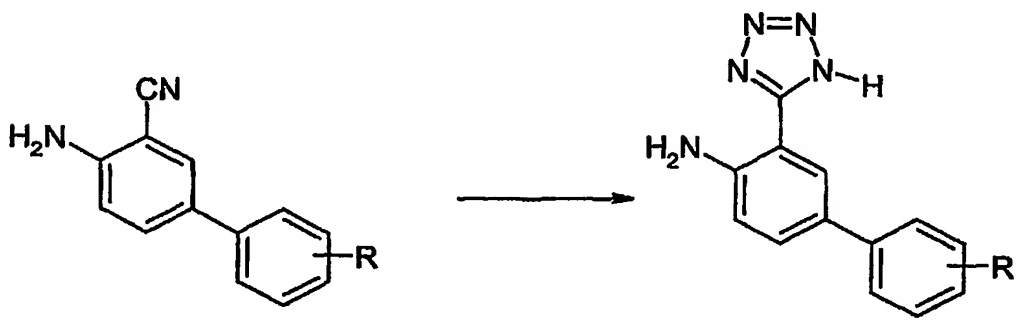
Example 1



4-Amino-4′-trifluoromethyl-biphenyl-3-carbonitrile: To dimethoxyethane (100 mL) and water (50 mL) was added 2-amino-5-bromo-benzonitrile (8.1 g), 4-trifluoromethyl-phenyl-boronic acid (8.6 g) and potassium carbonate (18.7 g), nitrogen was bobbled through the mixture for 10 minutes. Under a nitrogen atmosphere was bis(triphenyl-phosphine)palladium (II) chloride (0.3 g) added, the reaction mixture was heated at reflux overnight, then cooled to room temperature and added water (150 mL). The mixture was extracted with ethyl acetate, the organic phase was washed with water (50 mL) and brine (50 mL), then dried with magnesium sulfate and evaporated to an oil. The product was purified by column chromatography. Yield 8.36 g of white powder.

Similarly was made:
4-Amino-4′-chloro-biphenyl-3-carbonitrile.
4-Amino-4′-fluoro-biphenyl-3-carbonitrile.
4-Amino-4′-methyl-biphenyl-3-carbonitrile.
4-Amino-4′-trilfuoromethoxy-biphenyl-3-carbonitrile.
4-Amino-3′-triluoromethyl-biphenyl-3-carbonitrile.

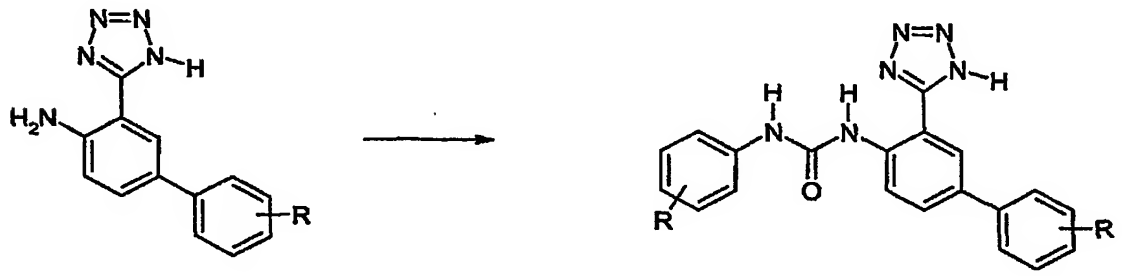
Example 2



3-(1*H*-Tetrazol-5-yl)-4′-trifluoromethyl-biphenyl-4-ylamine: 4-Amino-4′-trifluoromethyl-biphenyl-3-carbonitrile (8.3 g) was dissolved in toluene (100 mL), to the solution was added sodium azide (3.1 g) and triethylammonium chloride (6.6 g). The reaction mixture was heated at 60-62°C overnight, then cooled to room temperature and added water (40 mL), then hydrochloric acid (4 M, 13 mL) was added until pH = 1. The product precipitated and was isolated by filtration, the precipitate was washed with cold water and dried on the filter by sucking air through the compound. Yield 10.2 g of white powder.

Similarly was made:
4′-Chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-ylamine.
4′-Fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-ylamine.
4′-Methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-ylamine.
3-(1*H*-tetrazol-5-yl)-4′-trifluoromethoxy-biphenyl-4-ylamine.
3-(1*H*-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-ylamine.

Example 3



***N*-(4-Chloro-3-trifluoromethyl-phenyl)-*N*′-[3-(1H-tetrazol-5-yl)-4′-trifluoromethyl-biphenyl-4-yl]-urea:** 3-(1*H*-Tetrazol-5-yl)-4′-trifluoromethyl-biphenyl-4-ylamine (0.5 g) and 4-choro-3-trifluoromethyl-phenyl isocyanate (0.4 g) in toluene (15 mL) was stirred at room temperature for two days. The reaction mixture was evaporated to an oil, the oil was dissolved in acetone and filtrated through Celite, the filtrate was added water, the product precipitated and was isolated by filtration. Yield 0.6 g Mp. 226-228°C.

Similarly was made:
N-(3-Trifluoromethyl-phenyl)-*N*′-[4′-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 253-254°C.
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*′-[4′-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp.242-243°C.
N-(3,5-Dichloro-phenyl)-*N*′-[4′-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 231-234°C.

N-(3,5-Difluoro-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 250-251°C.

N-(3,5-Dichloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea: Mp. 226-230°C.

N-(3,5-Difluoro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea: Mp. 245-247°C.

N-(3-Trifluoromethyl-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-5-yl]-urea: Mp. 256-258°C.

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 247-249°C.

N-(3,5-Dichloro-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 241-243°C.

N-(3,5-Difluoro-phenyl)-*N'*-[4'-fluoro-2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 255-256°C.

N- (4-Fluoro-3-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea: Mp. 247-249°C (subl.).

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea: Mp. 246-248°C.

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 230-233°C.

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 243-245°C.

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 251-253°C.

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 253-254°C.

N-(2-Trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea: Mp. 240-243°C.

N-(2-Trifluoromethyl-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 256-258°C.

N-(2-Bromo-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea: Mp. 242-243°C.

N-(2-Trifluoromethyl-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 290-292°C.

N-(2-Bromo-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 255-256°C.

N-(2-Bromo-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 256-258°C.

N-(2-Fluoro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea: Mp. 251-252°C.

N-(2-Fluoro-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 257-259°C.

N-(2-Fluoro-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 263-264°C.

N-(2-Fluoro-phenyl)-*N'*-[4'-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 260-262°C.

N-(2-Chloro-phenyl)-*N'*-[4'-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 261-263°C.

N-(2-Bromo-phenyl)-*N'*-[4'-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 255-257°C.

N-(2-Trifluoromethyl-phenyl)-*N'*-[4'-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 259-261°C.

N-(2-Chloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea: Mp. 254-255°C (subl.).

N-(2-Chloro-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 255-257°C. (subl.).

N-(2-Chloro-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 255-257°C (subl.).

N-(3,5-Dichloro-phenyl)-*N'*-[4'-methoxy-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 200-201°C.

N-(3,5-Difluoro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethoxy-biphenyl-4-yl]-urea: Mp. 238-241°C.

N-(3,5-Dichloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethoxy-biphenyl-4-yl]-urea: Mp.224-225°C.

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethoxy-biphenyl-4-yl]-urea: Mp. 238-240°C (subl.).

N-(3,5-Difluoro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea: Mp. 255-257°C.

N-(3,5-Dichloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea: Mp. 236-239°C (subl.).

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea: Mp. 250-252°C.

N-(3,5-Difluoro-phenyl)-*N'*-[4'-methoxy-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 129-133°C.

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4'-methoxy-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea: Mp. 219-221°C.

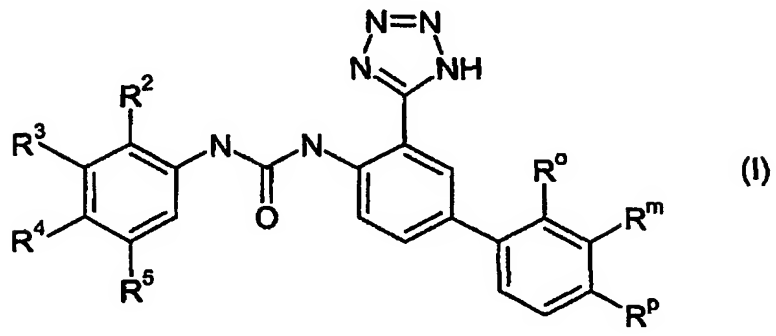
N-(3-Bromo-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea: Mp. 203-210°C (subl.).

N-(4-Chloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea: Mp. 232-234°C.

N- (4-Fluoro-3-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea: Mp. 254-255°C.

CLAIMS:

1. A chemical compound represented by general formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

R^o, R^m and R^p independently of each other represent
hydrogen, halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy;
with the proviso that not all three of R^o, R^m and R^p represent hydrogen;

R^2, R^3, R^4 and R^5 independently of each other represent
hydrogen, halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy;

with the proviso that the compound is not
N-(3-Trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea.

2. The compound of claim 1, wherein
R^o represents hydrogen;
R^m represents hydrogen; and
R^p represents halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy.

3. The compound of claim 1, wherein
R^o represents hydrogen;
R^p represents hydrogen; and
R^m represents halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy.

4. The compound of any one of claims 1-3, wherein
R^3, R^4 and R^5 represent hydrogen; and
R^2 represents halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy.

5. The compound of any one of claims 1-3, wherein
R^2, R^4 and R^5 represent hydrogen; and
R^3 represents halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy.

6. The compound of any one of claims 1-3, wherein
R^2, R^3 and R^5 represent hydrogen; and
R^4 represents halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy.

7. The compound of any one of claims 1-3, wherein
R^2 and R^5 represent hydrogen; and
R^3 and R^4 independently of each other represent halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy.

8. The compound of any one of claims 1-3, wherein
R^2 and R^4 represent hydrogen; and
R^3 and R^5 independently of each other represent halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy.

9. The compound of claim 1, being
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[3-(1H-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(3-Trifluoromethyl-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Dichloro-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Difluoro-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Dichloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(3,5-Difluoro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(3-Trifluoromethyl-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-5-yl]-urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Dichloro-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Difluoro-phenyl)-*N'*-[4'-fluoro-2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N- (4-Fluoro-3-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(2-Trifluoromethyl-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Bromo-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(2-Trifluoromethyl-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Bromo-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Bromo-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Fluoro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(2-Fluoro-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Fluoro-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Fluoro-phenyl)-*N'*-[4'-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Chloro-phenyl)-*N'*-[4'-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Bromo-phenyl)-*N'*-[4'-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Trifluoromethyl-phenyl)-*N'*-[4'-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Chloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(2-Chloro-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(2-Chloro-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Dichloro-phenyl)-*N'*-[4'-methoxy-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Difluoro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethoxy-biphenyl-4-yl]-urea;
N-(3,5-Dichloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethoxy-biphenyl-4-yl]-urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethoxy-biphenyl-4-yl]-urea;
N-(3,5-Difluoro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(3,5-Dichloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(3,5-Difluoro-phenyl)-*N'*-[4'-methoxy-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4'-methoxy-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3-Bromo-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(4-Chloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N- (4-Fluoro-3-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea;
or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1-9, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

11. The use of a compound according to any one of claims 1-9, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to the blockade of chloride channels.

12. The use according to claim 11, wherein the disease, disorder or condition responsive to the blockade of chloride channels is a bone metabolic disease, an osteoclast related bone disease, or a disease, disorder or condition that is responsive to inhibition of angiogenesis.

13. A method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to responsive to the blockade of chloride channels, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound according to any one of the claims 1-9, or a pharmaceutically acceptable salt thereof.